REMARKS

STATUS OF THE CLAIMS

Claims 66-71 and 125-128 are pending as shown above.

REJECTION WITHDRAWN

Applicants note that the rejection of claims 66-71 and 125-128 under 35 U.S.C. § 103(a) as allegedly obvious over Clontech in view of U.S. Patent No. 5,635,355 (hereinafter "Grosveld") has been withdrawn. (Office Action, page 3).

35 U.S.C. § 112, 1ST PARAGRAPH, WRITTEN DESCRIPTION

Claims 66-71 and 125-128 were newly rejected under 35 U.S.C. § 112, 1st paragraph on the grounds that the as-filed specification does not reasonably convey possession of the recitation "wherein there are at least two different insert sequences." (Office Action, pages 2-3).

Applicants traverse the rejection and supporting remarks.

It is axiomatic that the written description requirement is satisfied when the as-filed specification, in light of the knowledge possessed by the skilled artisan at the time of filing, reasonably conveys that Applicants were in possession of the claimed subject matter. *See, e.g., In re Lukach*, 169 USPQ 795, 796 (CCPA 1971); *In re Lange*, 209 USPQ 288 (CCPA 1981). Not only must the disclosure be read in light of the knowledge possessed by one of skill in the art, but the burden is on the Examiner to provide evidence as to why a skilled artisan would not have recognized that the applicant was in possession of claimed invention at the time of filing. *Vas Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991); *In re Wertheim*, 191 USPQ 90 (CCPA 1976).

As previously noted, it is implicit in the term "library" that there are at least two different (or distinct) inserts. This is also made clear in the as-filed specification. *See, e.g.,* page 46, line 29 to page 47, line 10; page 48, line 29 to page 49, line 8; Example 9, part D on page 114, emphasis added.

> As disclosed *supra*, accessible regions can be identified by any number of methods. Collections of accessible region sequences from a particular cell can be cloned to generate a library, and the nucleotide sequences of the members of the library can be determined to generate a database specific to the cell from which the accessible regions were obtained. Confirmation of the identification of a

cloned insert in a library as comprising an accessible region is accomplished, if desired, by conducting DNase hypersensitive site mapping in the vicinity of any accessible region sequence obtained by the methods disclosed herein. Co-localization of a particular insert sequence with a DNase hypersensitive site validates the identity of the insert as an accessible regulatory region. Once a suitable number of **distinct inserts** are confirmed to reside within DNase hypersensitive sites in vivo, larger-scale sequencing and annotation projects can be initiated. For example, a large number of library inserts can be sequenced and their map locations determined by comparison with genome sequence databases. For a given accessible region sequence, the closest ORF in the genome is provisionally assigned as the target locus regulated by sequences within the accessible region.

The libraries formed can represent accessible regions for a particular cell type or cellular condition. Thus, different libraries can represent, for example, accessible regions for: cells that express a gene of interest at a high level, cells that express a gene of interest at a low level, cells that do not express a gene of interest, healthy cells, diseased cells, infected cells, uninfected cells, and/or cells at various stages of development. Alternatively or in addition, such individual libraries can be combined to form a collection of libraries. Essentially any number of libraries can be combined. Typically, a collection of libraries contains at least 2, 5 or 10 libraries, or any integral value therebetween, or any integral value over 10; each library corresponding to a different type of cell or a different cellular state. For example, a collection of libraries can comprise a library from cells infected with one or more pathogenic agents and a library from counterpart uninfected cells. Determination of the nucleotide sequences of the **members** of a library can be used to generate a database of accessible sequences specific to a particular cell type.

To obtain a library of accessible region sequences, single-stranded extensions in the DNA fragments in the 100-200 bp **pool** (obtained as described above) are repaired by incubation with T4 DNA polymerase (New England Biolabs, Beverly, MA) and the four deoxyribonucleoside triphosphates; and aliquots of the end-repaired DNA are ligated into SmaI-linearized pBluescript II (Stratagene, La Jolla, CA) with a rapid ligation kit (Roche Molecular Biochemicals). Ligated material is transformed into XL1Blue competent E. coli (Stratagene, La Jolla, CA), and plated on IPTG- and X-gal-containing medium. Cells harboring insert-containing plasmids are grown into minicultures, plasmid DNA is purified from the minicultures, and the inserts are characterized by nucleotide sequencing.

Examples 10-12 also clearly teach that libraries include pool (or collections) of distinct fragments. Thus, it is clear that the skilled artisan would recognize that Applicants were in

possession of the claimed subject matter at the time of filing. However, if it would advance prosecution, Applicants would remove the phrase "wherein there are at least two different insert sequences" as it is implicit in the term library.

In sum, Applicants submit that the claimed subject matter is fully described by the as-filed specification and, as such, withdrawal of the rejection is in order.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the claims are now in condition for allowance and request early notification to that effect.

Respectfully submitted,

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